

REMARKS

Claims 1-16, 36 and 37 presently appear in this case. Claims 17-26 have been cancelled without prejudice toward the continuation of prosecution in a divisional application. No claims have been allowed. The official action of January 28, 2003, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for activating natural killer cells in a human patient by administering an effective amount of an adenosine A3 receptor agonist (A3RAg). The agonist will activate the NK cells by fully or partially activating the adenosine A3 receptors on the NK cells. This method may be used to treat diseases that are sensitive to activated NK cells, such as the treatment of tumor cells, malignant and infectious diseases, immunoregulation, hematopoiesis, reproduction and neuroendocrine interactions.

The examiner has repeated the restriction requirement and made it final, stating that claims 17-26 have been withdrawn from further consideration as being drawn to a non-elected invention.

Claims 17-26 have been cancelled without prejudice toward the continuation of prosecution in a divisional application.

The examiner has objected to the disclosure due to an error in the name of Cl-IB-MECA.

The inconsistency in the name of the compound as set forth at various places in the specification is acknowledged, and the examiner is thanked for bringing this to applicant's attention. The correct formula of Cl-IB-MECA is 2-chloro-N⁶-(3-iodobenzyl)-adenosine-5'-N-methyluronamide. This was well known to the art as of the effective filing date of the present application, for example, from Yao et al, Biochem Biophys Res Comm 232:317-322 (1997), which was cited in the International Search Report, and a copy of which is attached to the Information Disclosure Statement filed on even date herewith. The same error appears in the specification with respect to the name of IB-MECA. This is also 3-iodobenzyl, as can be seen from the same reference. The specification and claims have now been amended so that every instance reads as was correctly set forth at page 13, lines 7-8, of the present specification.

The specification has also been reviewed for other typographical and clerical errors, and all such errors that have been noted have now been corrected. Reconsideration and withdrawal of this objection are, therefore, respectfully urged.

Claims 1-16 and 27-35 have been rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for Cl-IB-MECA, does not reasonably provide enablement for methods to activate natural killer cells using any other A3RAg. The examiner states that undue

experimentation would be required to determine which A3RAg and what concentrations and specificity would be effective for activating natural killer cells. The examiner states that there is unpredictability in the art, and one working example is not sufficient to support the breadth of the claims.

Further, with respect to claims 9-16, the examiner states that while the specification is enabling for methods to activate natural killer cells using Cl-IB-MECA, hence enabling methods to treat various tumor cells in which NK cells are known to be cytotoxic, does not reasonably provide enablement for methods for a therapeutic treatment of any other disease or symptom of a disease. This rejection is respectfully traversed.

With respect to the examiner's statement there is only a single working example in the specification, attached hereto is a Declaration under 37 C.F.R. §1.132 by the present inventor that describes results with two additional A3RAg's, IB-MECA and MRS1898. In addition, the specification mentions a number of other A3 agonists, for example, at page 8, line 19, to page 9, line 2. It can be seen from this Declaration that the present invention can readily be expanded to other agonists without undue experimentation. The art is aware of many A3RAg's. The present specification contains one example, and the attached Declaration two others. As three of these have been shown to be active, there is no reason to believe that any other A3RAg would not also be operable in the present invention, nor is there good reason to believe that undue

experimentation would be involved in order to determine appropriate dosages, etc. This is well within the skill of one of ordinary skill in the art without undue experimentation.

Regarding claims 9-16, claim 9 has now been amended in order to better define the disease treated by the method of the invention. It must be a disease that is sensitive to activated NK cells. Furthermore, the claim sets forth specific diseases and conditions that fall within this category. As the examiner concedes that NK cells may be activated by means of the present invention and the claims now only read on the treatment of diseases that are sensitive to activated NK cells, the claims are not broader than the enabling disclosure. Support for the amendments to claim 9 may be found on page 1, lines 5-17; page 5, lines 1-3; and the Examples. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 1-16 and 28 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner states that the term "individual" in claims 1-16 is indefinite as it is unclear if the individual is limited to humans, mammals, animals and/or cells. The examiner also states that the phrase "sulfur or carbon atom" in claims 2, 10 and 28 render the claims indefinite as Y cannot simply be a carbon atom, as that would imply a bivalent carbon.

The claims have now been amended to specify that the individual is a human being, and the phrase "sulfur or carbon atom" has now been amended to clarify that Y is an oxygen or sulfur atom or is CH₂. Accordingly, this rejection has now been obviated. Reconsideration and withdrawal thereof are, therefore, respectfully urged.

Claim 1 has been rejected under 35 U.S.C. §102(b) as being clearly anticipated by Williams. The examiner states that Williams teaches that 2-chloroadenosine, an adenosine receptor agonist stimulates natural killer cells. This rejection is respectfully traversed.

Claim 1 has now been amended to better define the invention and to specify that the A3Rag activates the NK cells via the A3 receptor, "so as to fully or partially activate adenosine A3 receptors on said NK cells and so as to achieve activation of said NK cells." In Williams, on the other hand, 2-chloroadenosine (2CA) acts on the NK cells via a novel non-A1/A2/A3 cell surface receptor. See the abstract, where it states:

These data suggest that 2CA acts on NK cells via a novel (non-A₁/A₂/A₃) cell-surface receptor.

See also the paragraph bridging the left- and right-hand columns on page 190, the right-hand column on page 193, and the right-hand column on page 194. Furthermore, nowhere in Williams is it stated that 2CA is an A3 receptor agonist. On the contrary, reference is made to Barbieri et al, Neurochem

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Int 32:493-504 (1998), a copy of the abstract of which is attached, which states that 2CA appears to bind to A2a receptors and not to A3 receptors. Thus, the agonist disclosed by Williams does not fall within the scope of claim 1, and Williams does not anticipate claim 1. Reconsideration and withdrawal of this rejection are, therefore, also respectfully urged.

Claims 27-35 have been rejected under 35 U.S.C. §102(b) as being anticipated by US patent 5,773,423 to Jacobson.

Claims 27-35 have now been deleted, thus obviating this rejection.

Claims 1-16 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Williams and Jacobson. The examiner states that Williams teaches that 2CA is an adenosine receptor agonist that activates natural killer cells, but does not specifically teach Cl-IB-MECA. The examiner states that Jacobson teaches that modification of the adenosine at the 5' position and/or at the N⁶- position will moderate A₃ selectivity and, therefore, it would be obvious to modify the 2-chloroadenosine of Williams to enhance the activation of natural killer cells. This rejection is respectfully traversed.

As stated above, the invention as defined in the presently amended claims teaches activation of NK cells by A3 agonists via the A3 receptor. Williams does not disclose the

method of the invention and, in fact, teaches away from the method of the invention in that he explicitly teaches that 2CA does not stimulate NK cells through the A3 receptor nor through any other adenosine receptor. One of ordinary skill in the art would, therefore, have had no reason to combine Williams with Jacobson since Jacobson teaches modification of adenosine to moderate A3 selectivity, while Williams teaches away from adenosine receptor binding. Accordingly, the method of the present invention would not have been obvious from any combination of Williams and Jacobson. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

The examiner states that the two Priebe et al publications teach that modulation of natural killer cells can be achieved via the adenosine A₁ or A₂ receptor. The examiner recognizes that these references do not implicate the adenosine A3 receptor and the activation of natural killer cells.

These and the other references of record have been noted, as has the examiner's implicit recognition that they are insufficiently pertinent to warrant their application against the claims. It is further noted that neither Priebe reference mentions A3 receptors at all. Furthermore, the results presented are not unequivocal (see the first full paragraph in the left-hand column on page 4331 of the first Priebe et al publication), and the authors summarize that the

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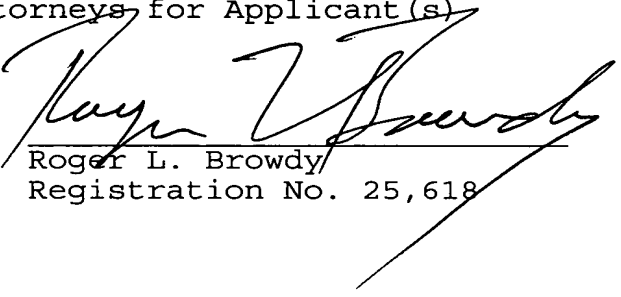
mechanism of stimulation and inhibition may not involve adenosine receptors (page 4331, last paragraph in left-hand column and right-hand column).

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are, therefore, earnestly solicited.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of Fishman, P.

Serial No. 09/832,818

Group Art Unit: 1623

Filed: April 12, 2001

Examiner: J. Young

For: **ACTIVATION OF NATURAL KILLER CELLS BY...**

DECLARATION
under Rule 132

Commissioner of Patents and Trademarks
Washington, D.C. 20231

I, Pnina Fishman, an Israeli citizen residing at 19 Asher Barash St., Herzliya, Israel, hereby declare:

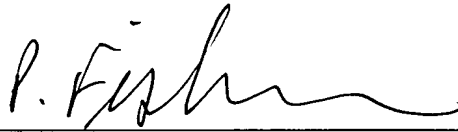
1. I am currently the CSO of Can-Fite BioPharma.
2. My list of publications is attached herewith as Annex "A". My fields of expertise include the field of adenosine receptors and more specifically the A3 adenosine receptor and the development of agonists to this receptor as drugs for the treatment of cancer and inflammatory diseases.
3. I am familiar with the above captioned application (hereinafter "*the application*"), and with the claims thereof. The invention relates to a method for activating NK cells using one or more adenosine A3 receptor agonists (A3RAg).
4. Although the application describes results with Cl-IB-MECA, I believe that these results are representative of the A3RAg group in general. In the following, I describe experimental results using two additional A3RAg, IB-MECA and MRS1898.
5. In the first experiment, mice were treated with IB-MECA and the activity test of the NK was conducted *ex vivo* on the murine splenocytes, as described in the application (pages 13-14). It may be seen from Fig. 1 (Annex B) that IB-MECA induces NK activity *in vivo*.
6. In the second experiment, murine splenocytes were incubated with MRS1898 and the ⁵¹Cr release assay was performed as described in the application. The results are presented in Fig. 2 (Annex C). It may be seen that only the low concentrations of 0.01, and 0.1 μ M potentiate the NK activity,

demonstrating the specificity of A3RAg activation in the NK cells in response to the A3 agonist.

7. I therefore believe that these results support the claims of the application that A3RAg activate NK cells.

8. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: June 11, 2003

A handwritten signature in black ink, appearing to read 'P. Fishman', written over a horizontal line.

Prof. Pnina Fishman

Annex A

Prof. Pnina Fishman, Ph.D.

LIST OF PUBLICATIONS

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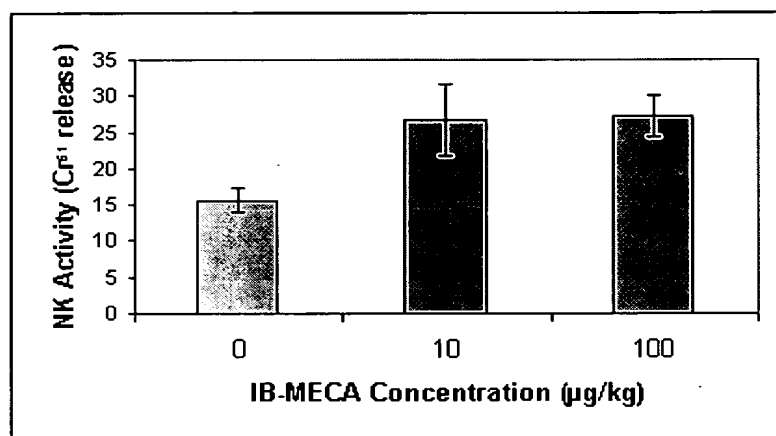
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Annex B

Annex C